Review

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Glutamatergic neurotransmission modulators as emerging new drugs for schizophrenia

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Schizophrenia is a neurodevelopmental mental disorder whose aetiology includes genetic and environmental factors. Because of its early onset, chronicity and characteristic interference with education, employment and socialisation, this illness represents a tremendous human and economic burden to those who suffer from it, their families and society as a whole. Conventional and atypical antipsychotics, which mainly affect dopaminergic and serotonergic neurotransmission, are currently the cornerstone of schizophrenia treatment. Although the introduction of atypical antipsychotics represents a major development and, overall, antipsychotics are efficacious against psychotic symptoms, there remains a critical unmet need for innovative medications with improved efficacy and tolerability for the negative symptoms and cognitive deficits associated with schizophrenia. These dysfunction domains are reliable predictors of long-term disability and treatment outcome and are presently viewed as crucial targets for new pharmacological treatments of schizophrenia. Within this medication development framework, the modulation of glutamatergic neurotransmission has become the focus of intense research. Glutamate (GLU)-mediated neuronal processes are critical throughout the brain and glutamatergic neurotransmission dysfunctions have been hypothesised to play a crucial role in schizophrenia pathophysiology. Glutamatergic neurotransmission may be modulated at multiple levels, with GLU receptor families and their subtypes representing a modulatory site-rich environment for drug research. Numerous types of neurotransmission modulators, acting at the NMDA, AMPA and metabotropic GLU receptors, and/or affecting GLU synaptic release, are hypothesised to be beneficial for schizophrenia treatment, and are presently in various stages of development. For some of these compounds, preliminary studies have furnished encouraging clinical data. Ongoing and planned research is expected to provide, in the near future, critical information regarding the practical utility and tolerability of glutamatergic approaches for schizophrenia pharmacotherapy.

Keywords: AMPAkines, cognitive deficits, GLU-release inhibitors, mGluR modulators, negative symptoms, NMDA receptor modulators, schizophrenia

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1. Background

Schizophrenia, which has long been considered the most chronic, debilitating and costly mental illness, is one of the most devastating human diseases, ranking among the top 10 causes of disability in developed countries worldwide. It affects ~ 1% of the world's population and generally manifest in late adolescence or early adulthood [1]. The core phenomenological features of schizophrenia include patterns of myriad symptoms, most of which fall into categories termed 'positive,' 'negative' and 'cognitive.' Positive symptoms generally imply awareness beyond normal experience;

negative symptoms generally reflect diminished experience. Cognitive or 'disorganised' symptoms refer to deficits in maintaining attention, perception, learning, memory and thinking on an abstract level. The positive symptoms of schizophrenia (e.g., agitation, delusions, hallucinations and grossly disorganised behaviour), being more easily identified and more likely to lead to hospitalisation, have been traditionally used as main determinants of patient outcome. However, the negative and cognitive components, although less florid, are usually much more pernicious. The negative symptoms are deficiencies in vital areas of human endeavour, including motivation, verbal and nonverbal communication, interest in socialisation, experiencing pleasure and expression of affect. They have a deleterious effect on performance at school or work and a destructive impact on relationships with friends and family, which usually leads to a removal of both focus and potential support networks from an individual's life. Thus, negative symptoms are consistently found to be predictors of family and community functioning, especially when compared with positive symptoms [2]. Intertwined with the negative/positive symptomatology, neurocognitive testing usually reveals a pattern of deficits suggestive of widespread dysfunction. Virtually all aspects of brain function, from basic sensory processes to the most complex aspects of thought, are affected to some extent. Overall, the widespread cognitive dysfunction characteristic of schizophrenia represents one of the main prognostic factors associated with the illness, and is presently considered a reliable predictor of long-term disability and treatment outcome [3].

The course of schizophrenia varies, but, despite treatment, most patients have a chronic course with frequent psychotic relapses characterised by exacerbation of positive symptoms and rehospitalisation. Most affected individuals have substantial lifelong impairment and more than half require continuous support, whether living in the community or in long-term institutions. Some 15% of patients reside for long periods in chronic mental health facilities and another 15% end up incarcerated for petty crimes and vagrancy. The standardised mortality ratio for persons with schizophrenia is significantly higher than in the general population, reflecting higher rates of both unnatural and natural death. The high prevalence of obesity, smoking and alcohol abuse in persons with schizophrenia contributes to this increased risk. The suffering of people with schizophrenia is further highlighted by a 9 – 13% lifetime risk of committing suicide, estimated to be 20- to 50-times higher than that of the general population. Overall, the economic costs imposed by schizophrenia on society are enormous. More than a third of mental hospital beds are occupied by schizophrenia patients. Direct and indirect costs for the treatment of this illness are estimated at $20 – 35 billion annually in the US alone; when the costs of lost production are included the estimated costs are > $46 billion [4].

Twin studies provide evidence of a genetic contribution to schizophrenia: if one identical twin has the disease, the other has an ~ 30 – 40% chance of developing it, even if the two have been brought up in different families. Nevertheless, the shared genes of identical twins are not sufficient to give rise to the disease in all instances, thus pointing to the involvement of additional factors [4]. On the other hand, the existence of multiple predisposing variants of genes (i.e., alleles) for schizophrenia may help explain the variability of symptoms across patients, reflecting perhaps, for different individuals, predominant effects on different brain neurotransmitter systems [5].

During the last 10 – 15 years, within the framework of the recognised importance of genetic vulnerability, the concept of schizophrenia as a 'functional' psychosis has changed to the current paradigm of schizophrenia as a neurodevelopmental disorder. The onset of the illness with substantial progression of symptoms during the first few years and later stabilisation, makes schizophrenia very unusual among brain disorders. The fact that most cases arise in early adulthood is also an important clue with respect to pathophysiology because developmental changes may continue to occur in the brain during this period. The neurodevelopmental hypothesis (NDH) of schizophrenia basically suggests that a disruption of brain development during early life underlies the later emergence of illness during adulthood, while neuropathological processes may contribute to deterioration and illness progression. Recent versions of the hypothesis have incorporated evidence from structural neuroimaging studies, which suggests changes in brain volumes after the onset of schizophrenia. More detailed models indicating that multiple insults are required over the lifespan rather than one single early-life event have replaced early versions of the NDH, which were based on a 'static encephalopathy' concept [6]. One of the most important conclusions stemming from recent research is that no single brain area is 'responsible' for schizophrenia and that there is no pathognomonic neuroanatomical or neuropsychological profile of schizophrenia, which probably reflects the aetiological heterogeneity within this disorder [7]. This concept is supported by evidence suggestive of defects in interneuronal connectivity in the frontal and temporal cortical and related subcortical regions of the brains of individuals with schizophrenia [4-7].

The cornerstone of schizophrenia treatment remains pharmacotherapy, which presently employs antipsychotic medications [8]. Historically, the principles guiding antipsychotic drug development have massively influenced the understanding of schizophrenia, while simultaneously undergoing a reshaping process in view of the emerging complexities associated with the biological foundation of this illness. For decades, theories of schizophrenia have focused on a single brain neurotransmitter, dopamine (DA), based primarily on the observation that all conventional antipsychotic drugs are characterised by antagonistic activity at DA D2 receptors and degrees of therapeutic efficacy that highly correlate with their affinity for striatal D2 receptors [9]. Over the past 15 years, a fundamental paradigm change – substantial, but incomplete, attenuation of D2 receptor function combined with blockade

or inverse agonism of serotonin 5-HT_2 receptor function – has furnished the theoretical background for the development of atypical, second-generation antipsychotics (SGAs) [10]. However, despite the significant progress made during the last decades, for most patients there is still an urgent need for the development of novel treatment strategies. Accumulating evidence indicates that it is highly unlikely that the constellation of symptoms that characterise schizophrenia may reflect dysfunctions of single neurotransmitter systems. Consequently, the development of novel antipsychotic drugs now takes place within the framework of a multifactorial hypothesis of schizophrenia aetiology in which, besides DA, additional neurotransmitters are implicated, and neurotransmitter interactions in complex neurocircuits systems are highlighted [11]. It is hoped that these efforts may lead to new pharmacological treatment modalities and improved compounds, specifically efficacious against schizophrenia symptom clusters.

Within this medication development framework, the modulation of glutamatergic neurotransmission has become the focus of intense research. Glutamate (GLU) is the primary excitatory neurotransmitter in the mammalian brain. Unlike DA, which plays an important role only in isolated regions, GLU-mediated functions are critical throughout the brain. Approximately 60% of neurons in the brain, including all cortical pyramidal neurons and thalamic relay neurons, utilise GLU as their primary neurotransmitter. As a result, virtually all corticofugal, corticocortical and thalamocortical neurotransmission in the brain is mediated by GLU. In light of the major role of glutamatergic pathways in the modulation of mood, cognitive processes and motor behaviour, their reciprocal interactions with monoaminergic networks and their intense innervation of corticolimbic structures and the basal ganglia, it is thus reasonably expected that pharmacological modulation of glutamatergic neurotransmission would be highly relevant to schizophrenia treatment.

GLU receptors are divided into two broad families. Ionotropic receptors are differentiated based on sensitivity to the synthetic GLU derivatives NMDA, AMPA and kainic acid (KA). Metabotropic glutamatergic receptors (mGluRs), which are G protein-coupled and mediate longer-term neuromodulatory effects of GLU, are divided into groups on the basis of effector coupling and ligand sensitivity. Each of the four classes of GLU receptors (NMDA, AMPA, KA and mGluRs) are derived from distinct gene families encoding a variety of subunits that can form various receptor/channel combinations with a broad range of characteristics [12]. These GLU receptor families and their subtypes represent a modulatory site-rich environment for drug research and have increasingly become, during the last decade, the molecular targets for the development of innovative therapeutic agents in schizophrenia.

2. Medical need

Treatment resistance in schizophrenia remains a complex mental health problem. The tremendous human suffering and costs that continue to be generated by this illness reflect, at least in part, the inadequacies of the arsenal of medications presently available. Overall, both conventional and the newer, atypical antipsychotics do not reduce psychotic symptoms in all patients and have limited efficacy against negative symptoms and cognitive deficits that are increasingly conceptualised as cardinal features of schizophrenia. Patients with persistent positive symptoms still account for 20 – 30% of the people who have chronic schizophrenia [13]. Furthermore, the limited clinical effectiveness of available treatments against negative and cognitive symptoms undermines further efforts to rehabilitate the patients and limit chronicity [14]. Meta-analytic techniques suggest that patients with schizophrenia perform 0.5 – 1 standard deviations below the normal mean in numerous areas of neurocognition [15]. Neurocognitive impairment is associated with key features of schizophrenia, such as the inability to acquire skills, poor social problem solving and poor community functioning [3,16], and may actually represent a stronger correlate of poor outcome than any other symptom domain [3]. Consequently, neurocognitive performance has come to be viewed as a crucial target for pharmacological treatments for schizophrenia.

An additional liability, long known to be associated with conventional neuroleptics and presently suggested also in relation to some newer, atypical antipsychotics, is the induction of various types of side effects that may interfere with treatment, lead to decreased compliance and contribute to comorbidity and mental and physical disability. Thus, overall, for many patients there still is a great need for the development of treatment strategies that may offer improved tolerability and additional therapeutic benefits.

2.1 Existing treatments

Antipsychotic medications (Table 1) are the mainstay of pharmacological treatment for schizophrenia and psychotic disorders in general. At present, this type of medication includes conventional antipsychotics (or neuroleptics), which are also termed first-generation antipsychotics, and atypical antipsychotics, which are also termed SGAs. Additional types of psychotropic drugs used in schizophrenia as adjuvants to antipsychotics in order to increase efficacy or combat side effects, include lithium carbonate, anticonvulsants (e.g., carbamezepine, valproate), benzodiazepines and anticholinergic drugs.

Both clinical practice and research indicate that, in general, conventional antipsychotics do not adequately alleviate negative and affective symptoms and cognitive impairments [17]. A debate continues as to whether this type of drug can actually contribute to these symptom domains. A recent meta-analysis [18] reevaluates previous data and suggests that typical antipsychotics may provide modest-to-moderate gains in multiple cognitive domains, when compared with placebo. On the other hand, it has been highlighted that most studies showing brain shrinkage in schizophrenia were performed in patients receiving high D2 occupancy antipsychotic drugs, and recent longitudinal data of adult patients receiving newer, atypical

Table 1. Commonly used conventional and atypical antipsychotics.

	Generic name	Trade name	Year of US FDA approval
Conventional antipsychotics	Chlorpromazine	Thorazine	1953
	Perphenazine	Trilafon	1958
	Trifluoperazine	Stelazine	1958
	Fluphenazine	Prolixin	1959
	Thiothixene	Navane	1967
	Haloperidol	Haldol	1967
Atypical antipsychotics	Clozapine	Clozaril	1989
	Risperidone	Risperdal	1993
	Olanzapine	Zyprexa	1996
	Quetiapine	Seroquel	1997
	Ziprasidone	Geodon	2001
	Aripiprazole	Abilify	2002

antipsychotics suggest that no shrinkage occurs over time in these patients [19].

The spectrum of side effects induced by conventional antipsychotics extends beyond possible deleterious effects on schizophrenia symptomatology. Neuroleptic-induced extrapyramidal side effects (EPS) are characteristically associated with most conventional antipsychotics and may emerge in up to 75% of patients treated with these medications [20]. Additional debilitating side effects contribute to a high degree of noncompliance. Symptoms of pharmacogenic anhedonia, akinetic depression or neuroleptic-induced deficit syndrome are barely measurable on objective rating scales and are difficult to differentiate from the negative symptoms of schizophrenia [21]. Hyperprolactinaemia may result in galactorrhoea and sexual dysfunction, and weight gain can impact on a patient's self-esteem and increase the risk of patients developing a variety of disorders such as coronary heart disease or diabetes [22].

The introduction of atypical antipsychotics during the last two decades represents a major development in the treatment of schizophrenia and has provided basic and clinical data allowing for the steady evolution of the DA hypothesis of schizophrenia from one involving only DA receptors to one that includes interactions with multiple DA receptor subtypes (e.g., D3 and D4) and other neurotransmitter receptors. In general, atypical antipsychotics are considered at least as effective as classical neuroleptics in combating positive symptoms of schizophrenia. However, their claimed advantages for the treatment of negative symptoms and cognitive deficits are less established. Many studies comparing atypical antipsychotics with conventional antipsychotics have found the atypical agents to be superior for the treatment of negative symptoms, affective symptoms and cognitive deficits [23,24]. Nevertheless, it is a matter of debate whether the atypical agents have a direct effect on primary negative symptoms (i.e., those negative symptoms intrinsic to schizophrenia) or an indirect effect mediated by an improvement in the putative causes of secondary negative symptoms, such as medication side effects, inadequate social stimulation, unrecognised depression and/or intrusion of positive symptoms. Recent considerations, such as the importance of the dose of typical antipsychotic comparators, have called into question whether atypical antipsychotics actually improve cognition or whether they simply afford a release from the deleterious effects, such as EPS, of inappropriately large doses of typical antipsychotics (usually haloperidol) and concomitant adjunctive agents such as anticholinergics [23,24].

The most solidly demonstrated and recognised advantage of SGAs is that they are associated with a lower liability for EPS and a reduced risk of tardive dyskinesia [25,26]. This improved tolerability profile is probably one of the main factors guiding present shifts from conventional to atypical antipsychotics in overall antipsychotic drugs consumption. However, SGAs are not devoid of problematic side effects and clinical and research interest has recently focused on metabolic and endocrine dysfunctions that may be induced by some of the presently used atypical antipsychotics [27,28].

Clozapine, the first atypical antipsychotic, introduced in clinical practice in the early 1970s, probably represents the only presently available antipsychotic having a truly unique therapeutic profile. Clozapine is a unique prototype atypical, tricyclic, dibenzodiazepine-derivative antipsychotic agent. It has been proved to be effective and significantly superior to conventional neuroleptics in controlled studies in treatment-resistant schizophrenia, is presently the most effective antipsychotic for severely ill hospitalised patients and has been found to produce a very low incidence of motor side effects [29]. However, clozapine is associated with a relatively high risk for seizures, with potentially life-threatening agraunlocitosis in 1 – 2% of patients, requiring long-term monitoring of the neutrophil count [30], and with significant weight gain [27,28]. These drawbacks weigh heavily when risks and benefits of clozapine use are analysed. For example, using Framingham

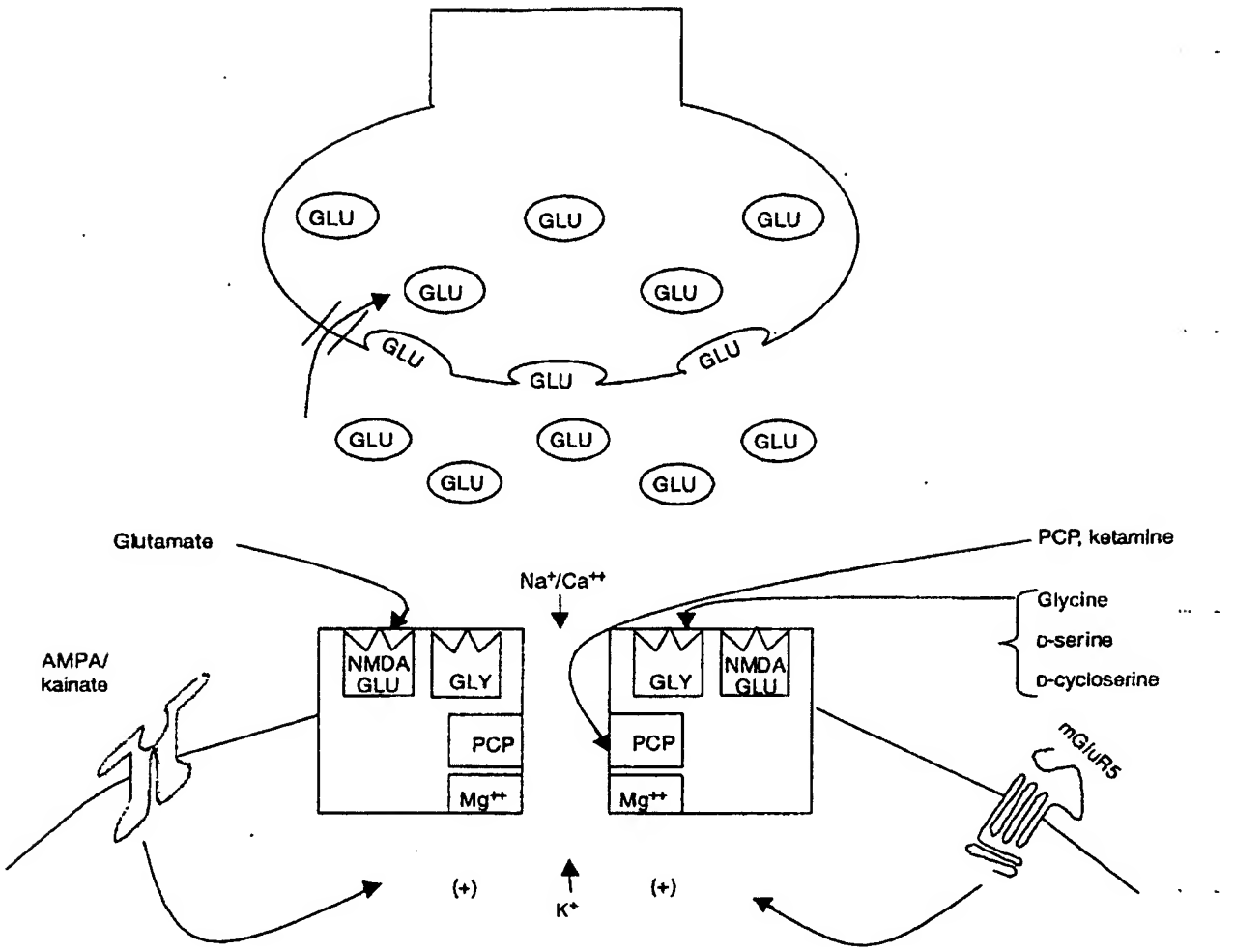


Figure 1. Simplified schematic diagram of a generic glutamatergic synapse. GLU is released from the presynaptic terminal and acts on ionotropic (NMDA, AMPA/kainate) and metabotropic (represented by mGluR5) GLU receptors. NMDA receptor is embedded in a postsynaptic structure that produces a tight coupling with other GLU receptors. Activation of AMPA/kainate and/or mGluR5 receptors can result in potentiation of NMDA receptor function. GLY, GLU/NMDA and PCP binding sites of the NMDA receptor are illustrated.
GLU: Glutamate; GLY: Glycine; mGluR5: Group 5 metabotropic GLU receptors; PCP: Phencyclidine.

Heart Study data, Fontaine *et al.* [31] estimated that although clozapine decreased suicidal behaviour in 492 of 100,000 schizophrenia patients over a 10-year period, the weight gain induced by clozapine would be expected to result in 416 additional deaths.

3. Current research goals

In view of the limitations of existing treatments and given the recent developments in the understanding of pathophysiological processes associated with schizophrenia, current research in the therapeutics of this illness focuses on the development of compounds characterised by mechanisms of action different than those of presently available antipsychotics.

The main clinical goals for the development of new therapeutic agents for schizophrenia include the following:

- superior efficacy, versus drugs used at present, against negative symptoms
- superior efficacy, versus drugs used at present, against cognitive deficits
- prevention of disease and disability progression
- preserved or improved efficacy against positive symptoms
- improved therapeutic index (i.e., less toxicity in relation to obtained benefits)
- avoidance of motor and/or metabolic side effects
- lack of detrimental interactions with other drugs, including presently used antipsychotics with which they may be coprescribed

It is hypothesised that beyond the traditional measures of symptomatology, achievement of these goals would necessarily lead to:

- increased levels of recovery
- decreased cumulative morbidity
- lower relapse rates
- better long-term outcome

4. Scientific rationale

Schizophrenia is currently the best established of the potential therapeutic targets for modulation of glutamatergic neurotransmission. NMDA, and also non-NMDA glutamatergic receptors, play an important role in a variety of cardinal brain functions, including memory and learning, synaptic and developmental plasticity, sensory information and coordinated movement patterns, which appear to be disturbed in schizophrenia [32]. Postmortem studies have identified abnormalities of GLU receptor density and subunit composition in the prefrontal cortex, thalamus and temporal lobe – areas that exhibit impaired activation during performance of cognitive tasks in schizophrenia. These findings suggest that glutamatergic dysregulation may occur in regionally specific subpopulations of glutamatergic receptors and support the potential value of a glutamatergic model for guiding research into the pathophysiology and treatment of schizophrenia. Glutamatergic receptor dysfunction could also play a role in neuroarchitectural abnormalities that have been described in schizophrenia, such as aberrant neuronal migration or reduced synaptic connection, due to the role of glutamatergic receptors in regulating neuronal migration, neurite outgrowth, synaptogenesis, and the 'pruning' of supernumerary neurons by apoptosis [5,6,33,34].

Because an extensive and functionally diverse range of GLU receptor subtypes are genetically encoded and can interact with environmental stressors during brain development, the model of glutamatergic dysfunction may account for the interplay of genetic and environmental risk factors identified in schizophrenia. Furthermore, dysfunction of glutamatergic neuronal systems is not inconsistent with the DA hypothesis of schizophrenia because reciprocal synaptic relationships between forebrain dopaminergic projections and glutamatergic systems have been well described. A relative increase in dopaminergic activity and/or a relative decrease in glutamatergic transmission could precipitate psychosis. This interaction between glutamatergic and dopaminergic systems suggests that the dopaminergic hyperactivity observed in schizophrenia may actually be secondary to deficits in glutamatergic neurotransmission [11].

The strongest line of evidence in support of an NMDA receptor hypofunction hypothesis of schizophrenia is based on the psychomimetic effects of phencyclidine (PCP), ketamine and other noncompetitive antagonists of NMDA receptor-mediated neurotransmission. These agents induce schizophrenia-like psychotic symptoms in normal volunteers and re-emergence of presenting symptoms in remitted patients. Unlike amphetamine, which stimulates DA release in the brain and can induce hallucinations and delusions in habitual users, NMDA receptor antagonists can also induce negative symptoms, thought disorder and cognitive dysfunction similar to that observed in schizophrenia [5,10,33,34].

PCP and ketamine induce these behavioural effects by binding to the PCP site located within the ion channel associated with the NMDA receptor (Figure 1). Their binding to this site leads to noncompetitive blockade of NMDA receptor-mediated neurotransmission, indicating that endogenous NMDA receptor dysfunction may play a critical role in the pathophysiology of schizophrenia. Moreover, competitive NMDA receptor antagonists (e.g., 3-[2-carboxypiperazin-4-yl]-propyl-1-phosphonic acid, CGS-19755) that block NMDA receptor by acting at the NMDA, rather than PCP recognition site, also appear to induce PCP-like effects in humans [35]. These findings are in agreement with the concept of NMDA receptor hypofunction in schizophrenia and led to the hypothesis that this phenomenon may not be PCP receptor-specific, but could result from a dysfunctional blockade of the NMDA receptor–ionophore complex [36]. The ability of NMDA receptor antagonists to induce schizophrenia-like symptoms and cognitive deficits suggests that enhancement of NMDA receptor-mediated neurotransmission may significantly ameliorate such symptom domains in schizophrenia.

It is also hypothesised that by facilitating NMDA receptor-related neuroplasticity, drugs that facilitate NMDA receptor function will increase the capacity of cortical networks to undergo experience-dependent modification [10]. This could be achieved either with compounds directly modulating NMDA receptor function (e.g., NMDA receptor agonists) or with modulators of other types of GLU receptors (i.e., AMPA and mGluRs) that may help increase the level of neural network activity and enhance the voltage-dependent recruitment of NMDA receptors (Figure 1) [37].

Alternative, but not mutually exclusive, glutamatergic models highlight the possible role of excessive GLU release and excitotoxicity in schizophrenia [10,12]. Following acute treatment, NMDA receptor antagonists stimulate prefrontal GLU release, which may independently induce schizophrenia-like impairment in cognitive performance [33]. NMDA receptor antagonists may also induce neurodegeneration of pyramidal neurons following acute or chronic administration. In this model, it is proposed that symptoms of schizophrenia do not reflect acute NMDA receptor blockade, but rather apoptotic changes that are associated with excessive GLU release and occur in susceptible brain regions, particularly frontocingulate areas [36]. Overall, these findings stress the importance of exploring the blockade of dysfunctional GLU release as an additional pharmacological strategy to be used in schizophrenia. Moreover, they suggest that regional imbalances and/or dysfunctional attempts to reach homeostasis may occur in schizophrenia. This hypothesis may be consistent with

Box 1. Types of glutamatergic neurotransmission modulators under development/evaluation for schizophrenia treatment.

NMDA receptor

- glycine site full agonists
- glycine site partial agonists
- glycine/D-serine transport inhibitors

AMPA receptor

- positive allosteric modulators (AMPAkines)

Metabotropic receptors

- group I metabotropic receptor (mGluR1, mGluR5) modulators
- group II/III metabotropic receptor modulators

Ion-channel blockers/glutamate release inhibitors

- lamotrigine (Lamictal®, GlaxoSmithKline)
- riluzole (Rilutek®, Aventis Pharma AG)

postmortem data indicating that the same individual with schizophrenia may manifest deficient glutamatergic innervation in one brain region and excessive innervation in another [38].

5. Competitive environment

Numerous neurotransmission modulators that act at diverse types of brain GLU receptors and/or affect GLU synaptic release are hypothesised to be beneficial in schizophrenia treatment. This section reviews the types of glutamatergic agents that are presently under development (Box 1) and highlights those compounds that have been assessed in clinical trials (Table 2).

5.1 NMDA receptor modulators

NMDA receptors are the most complex of the ionotropic GLU receptors and a primary drug development target for schizophrenia treatment. In addition to the recognition site for GLU, NMDA receptor contains a neuromodulatory site for glycine (GLY) that affects channel open time and desensitisation rate in the presence of agonist (GLU), but does not itself induce channel opening (Figure 1). As such, chronic GLY treatment in rodents has been found not to induce excitotoxicity [39,40]. NMDA receptors are blocked in a voltage sensitive manner by Mg^{2+}, which binds to a site within the NMDA receptor ion channel. As a result, NMDA receptors are uniquely voltage- as well as ligand (GLU)-sensitive, which permits them to participate in multiple neurocognitive processes, including long-term potentiation, nonlinear amplification, coincidence detection and attentional gating [32].

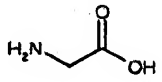
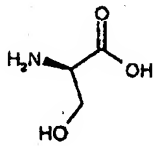
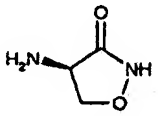
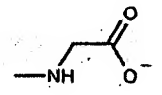
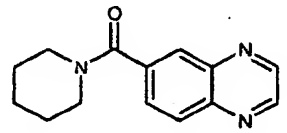
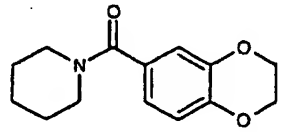
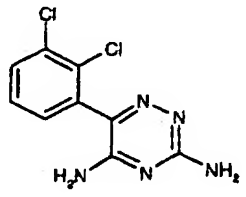
So far, the NMDA receptor site that has been explored most efficiently for drug development is the NMDA receptor-associated GLY site. A first-generation approach to potentiation of NMDA receptor-mediated neurotransmission *in vivo* has been the administration of the amino acids GLY and D-serine (DSR), which serve as endogenous modulators of the NMDA receptor complex. A more recent approach has been the targeting of amino acid transporters that regulate amino acid levels *in vivo*, analogous to use of selective serotonin reuptake inhibitors, rather than exogenous tryptophan administration to modulate brain serotonin levels in depression.

5.1.1 *NMDA receptor – GLY site agonists*

Clinical trials in schizophrenia have been conducted with the endogenous ligands GLY and DSR [101-104] that function as full agonists at the GLY site. Based on the known ability of these amino acids to stimulate NMDA receptor *in vitro* [12] it was predicted that additional GLY site ligands such as D-alanine or their precursors should also be effective in the treatment of schizophrenia [41,103]. Both GLY and DSR cross the blood–brain barrier and so can be administered systemically. GLY, however, is extensively metabolised in the periphery and large doses must be given to rodents (0.8 – 1.6 g/kg) and humans (0.4 g/kg i.v.; 0.8 g/kg p.o.) in order to significantly affect brain GLY levels [12,33,41]. DSR is nephrotoxic in rats; however, this effect is species-specific and does not seem to generalise even to other rodent species [42]. Physiologically, the GLY binding site appears to be approximately half-saturated under physiological circumstances, so that saturation of this site by exogenous compound or GLY/DSR transport inhibitors may lead to approximate doubling of NMDA receptor-mediated neurotransmission [12]. In addition to endogenous ligands, the synthetic GLY site agonist D-cycloserine (DCS) has been assessed clinically. DCS [105] is an antituberculosis drug that fortuitously crossreacts with the NMDA receptor GLY site. Although DCS crosses the blood–brain barrier readily, it functions only as a partial agonist, with 30 – 60% of the efficacy of GLY or DSR [12,33].

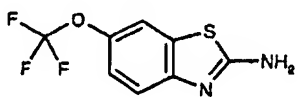
All clinical trials with GLY site agonists performed so far have employed these agents as adjuvants to ongoing treatment with conventional neuroleptics, clozapine or newer atypical antipsychotics (i.e., olanzapine and risperidone). Overall, GLY has been found to be effective at doses of 30 – 60 g/day (0.4 – 0.8 g/kg/day); DSR is effective at a dose of 2.1 g/day (30 mg/kg/day) and DCS at a dose of 50 mg/day. With both GLY and DSR, the effectiveness of higher doses has not been explored, so maximal benefit obtainable from GLY-site stimulation is unknown [12,33]. DCS was found to have a narrow therapeutic window: doses < 50 mg/day are ineffective, whereas doses > 100 mg/day cause symptom exacerbation due to emergent NMDA receptor antagonist effects [43]. In a retrospective comparison among schizophrenia patients who participated in controlled trials of both GLY and DCS, the degree of improvement was found to be significantly larger during GLY than DCS treatment on both an individual subject and group level [44]. Nevertheless, using functional magnetic resonance imaging, it was shown that patients receiving DCS, but not

Table 2. Competitive environment

Compound	Company	Structure	Stage of development	Mechanism of action
Glycine	Glytech		Phase II	NMDAR-GLY site full agonist
D-serine	Prestwick Pharmaceuticals		Phase II	NMDAR-GLY site full agonist
D-cycloserine (seromycin)	GD Searle		Phase II	NMDAR-GLY site partial agonist
Sarcosine (*N*-methylglycine)	Prestwick Pharmaceuticals		Phase II	GLYT1 inhibitor
CX-516	Cortex Pharmaceuticals Organon		Phase II	AMPA receptor positive modulator
CX-717*	Cortex Pharmaceuticals Organon		Phase II	AMPA receptor positive modulator
Lamotrigine (Lamictal®)	GlaxoSmithKline		Phase II	Ion-channel blocker/ GLU release inhibitor

*Outcome of first clinical trials in schizophrenia – pending.
GLU: Glutamate; GLY: Glycine; GLYT1: GLY type 1; NMDAR: NMDA receptor.

Table 2. Competitive environment (continued)

Compound	Company	Structure	Stage of development	Mechanism of action
Riluzole* (Rilutek®)	Aventis Pharma AG		Phase II	Ion-channel blocker/ GLU release inhibitor

*Outcome of first clinical trials in schizophrenia – pending.
GLU: Glutamate; GLY: Glycine; GLYT1: GLY type 1; NMDAR: NMDA receptor.

placebo, during a verbal cognitive challenge paradigm, demonstrate significant increase in temporal lobe activation that correlates with negative symptom amelioration [45].

A meta-analysis of the first 16 randomised, controlled trials with GLY, DSR and DCS (n = 343), obtained from the Cochrane Schizophrenia Group's Register of Trials, indicated that GLY and DSR, but not DCS, are effective in reducing negative symptoms of schizophrenia [46]. This analysis included diverse GLY site agonists doses and types of ongoing antipsychotic medications. Furthermore a characteristic pattern of therapeutic effects emerges from the outcome of studies performed so far in which identical GLY, DSR and DCS doses were used in conjunction with conventional neuroleptics, olanzapine and risperidone, or clozapine (Table 3). The most significant therapeutic benefits, covering not only negative, but also the cognitive and positive, symptom clusters, were achieved when the full agonists GLY and DSR were added to conventional neuroleptics. Similar, but less significant, effects were achieved when these compounds were used in conjunction with risperidone and/or olanzapine. Whether greater reductions occur during long-term treatment, or whether tolerance develops, is currently unknown. In some, but not all, studies, degree of negative symptoms improvement correlated significantly with baseline GLY levels, thus suggesting that patients with lowest pretreatment levels respond best to NMDA receptor agonist treatment [33].

In contrast, the addition of GLY and DSR to clozapine did not result in significant symptom changes, whereas the addition of DCS to treatment with this drug has actually resulted in a worsening of negative symptoms (Table 3). Because DCS functions as a GLY site agonist in the presence of low GLY concentrations, and as an antagonist in the presence of high concentrations [12,33], a likely explanation for the DCS-induced worsening of symptoms is that clozapine may already increase synaptic GLY levels. Recently, clozapine has been shown to block GLY and glutamine transport mediated by small neutral amino acid-like synaptosomal transporters (SNATs), providing a potential mechanism for both its unique therapeutic profile and the differential effects of NMDA receptor agonists in the presence of clozapine versus other antipsychotics [58].

Larger-scale, Phase II adjuvant treatment trials with GLY site agonists are presently in various stages of completion. A preliminary, total sample results analysis of a US National Institute of Mental Health (NIMH)-sponsored multi-centre study (CONSIST) comparing GLY and DCS effects did not indicate any significant therapeutic benefits of either GLY or DCS treatment [59]. A Stanley Foundation-sponsored multi-centre study (IMSER) performed in Israel is presently examining DSR adjuvant treatment effects in schizophrenia patients.

5.1.2 *Amino acid transport inhibitors*

Both GLY and DSR must be given at gram-level doses to significantly elevate CNS levels. An alternative approach to increase their CNS levels is the use of transport inhibitors, which raise their synaptic levels by preventing their removal from the synaptic cleft. Levels of synaptic GLY are tightly controlled by several transporters, including type I (GLYT1) and II (GLYT2) GLY transporters and system A-family SNAT transporters that serve to maintain low, subsaturating GLY concentrations in the immediate vicinity of the NMDA receptor complex [12,60]. GLYT1 and SNAT transporters predominate in the forebrain; GLYT1 transporters are closely associated with NMDA receptors, whereas GLYT2 transporters are co-localised with strychnine-sensitive inhibitory GLY receptors in the hindbrain. By increasing synaptic GLY concentration in the vicinity of NMDA receptors, blockers of GLYT1 are expected to facilitate glutamatergic neurotransmission, and as such represent promising targets for pharmacological intervention against schizophrenia [12,60,61]. System A transporters are expressed in both neurons and glia, and transport a range of small neutral amino acids (e.g., serine, proline, glutamine) along with GLY. Blockade of these transporters, therefore, would also be expected to increase synaptic levels of amino acids relevant to glutamatergic function. Mechanisms underlying regulation of synaptic DSR levels in the brain are still poorly understood. Traditional transport systems show limited affinity for DSR, although selective high-affinity DSR transporters have recently been described. As with GLY transporters, these may represent selective targets for the modulation of brain DSR levels [14].

The use of GLY transport inhibitors (GTIs) for treatment of persistent symptoms of schizophrenia was first proposed in

Table 3. Patterns of symptoms change following addition of identical doses of GLY, DSR and DCS to conventional and atypical antipsychotic drugs for schizophrenia treatment.

Study	Treatment, daily dose	N	Study duration (weeks)	Symptom clusters outcome,%* (p)		
				Positive	*Negative*	*Cognitive*
Conventional antipyschotic drugs						
Heresco-Levy *et al.* (1999) [47]	GLY, 60 g	22‡	6	-20 (NS)	-39 (< 0.001)	-24 (0.01)
Tsai *et al.* (1998) [48]	DSR, 2.1g	29	6	-21.9 (0.004)	-20 (< 0.001)	-17.7 (0.004)
Goff *et al.* (1999) [49]	DCS, 50 mg	47	8	NS	-23 (< 0.02)	NS
Heresco-Levy *et al.* (2002) [50]	DCS, 50 mg	8‡	6	NS	-14 (< 0.05)	NS
Risperidone, olanzapine						
Heresco-Levy *et al.* (2004) [51]	GLY, 60 g	17‡	6	-11.4 (0.006)	-23 (< 0.0001)	-9.2 (0.02)
Heresco-Levy (2005) [52]	DSR, 2.1 g	23‡	6	-13 (0.001)	-16 (< 0.001)	-11.7 (0.001)
Evins *et al.* (2002) [53]	DCS, 50 mg	10	8	NS	-10 (0.02)	NS
Heresco-Levy *et al.* (2002) [50]	DCS, 50 mg	8‡	6	NS	-14 (0.05)	NS
Clozapine						
Evins *et al.* (2000) [54]	GLY, 60 g	27	8	NS	NS	NS
Diaz *et al.* (2001) [55]	GLY, 60 g	12	14	NS	NS	NS
Tsai *et al.* (1999) [56]	DSR, 2.1 g	20	6	-3.6 (NS)	-2.5 (NS)	-0.8 (NS)
Goff *et al.* (1999) [57]	DCS, 50 mg	17‡	13	NS	+13§ (< 0.005)	NS

*Mean percentage change in symptom scale scores; ‡Crossover study; §Positive value represents worsening of symptoms.
DCS: D-cycloserine; DSR: D-serine; GLY: Glycine; NS: Not significant.

1997 based on the behavioural actions of the GLY derivative glycyldodecylamide (GDA) [61]. GDA inhibits GLY transport at concentrations relevant to its behavioural actions, and subsequent studies using a series of GLY derivatives demonstrated that their potency in reversing PCP-induced hyperactivity correlated closely with potency in GLY transport inhibition [62]. Recently, several GLYT1 inhibitors – for example, *N*-(3-[4'-fluorophenyl]-3-[4'-phenylphenoxy]propyl) sarcosine (Allelix Neuroscience), ORG-24598 (Organon Laboratories) and SSR-504734 (Sanofi-Synthelabo) – have been reported to possess the preclinical profile of putative antipsychotics [60,61], but data for each compound are generally scant and none of these compounds has yet been developed clinically.

So far, the only clinical data concerning GTIs derives from two studies performed in Taiwan with the canonical *in vitro* inhibitor of GLYT1-mediated transport: GLY-derivative sarcosine (*N*-methylglycine) [104]. In a 6-week, controlled trial with chronic schizophrenia patients, sarcosine 2 g/day adjuvant treatment led to 17 ($p < 0.0001$), 14 ($p < 0.0001$) and 13% ($p < 0.0001$) reductions in positive, negative and cognitive symptoms, respectively, without inducing any significant side effects [63]. In a recently completed study [64] 65 risperidone-treated schizophrenia in-patients suffering from acute exacerbations were enrolled in a 6-week, randomised, double-blind trial comparing sarcosine 2 g/day, DSR 2 g/day and placebo. Patients who received sarcosine plus risperidone were reported to show significantly more symptoms improvement than the other two treatment groups. Cotreatment with DSR and risperidone did not differ significantly from risperidone monotherapy in this patient population.

Preclinical and clinical development of GLYT1 inhibitors is currently being pursued by major pharmaceutical companies [14,60,61]. In order to obtain increased efficacy and to lower required daily doses below the gram-level employed with sarcosine, lead GLYT1 inhibitors proposed for clinical testing show ~ 1000-fold greater potency than sarcosine at the GLYT1 transporters along with > 1000-fold selectivity versus other CNS targets [61]. The development of DSR reuptake inhibitors and alanine-serine-cysteine transporter 1 inhibitors [106] for the treatment of schizophrenia and other neuropsychiatric disorders is also being pursued.

5.2 AMPA receptor modulators

AMPA receptor modulators may provide an alternative strategy to NMDA receptor-GLY site stimulation for enhancing NMDA receptor function and facilitating glutamatergic

neurotransmission. GLU activation of AMPA receptors is thought to mediate fastest synaptic neurotransmission in the brain. AMPA receptors are composed of combinations of GluR1 – 4 subunits and work synchronically with NMDA receptor, providing the primary depolarisation necessary to unblock NMDA receptors and to permit calcium entry into the cell. Synergistically, Ca^{2+} entry through unblocked NMDA receptors triggers AMPA insertion into the postsynaptic density and synaptic strengthening [65].

Ligands bind to AMPA receptors by competing with GLU at the GLU binding site, or noncompetitively at other sites (allosteric modulators). Selective, high-potency AMPA antagonists have been developed and may be effective in conditions such as stroke or epilepsy, which are characterised by hyperglutamatergia. A distinct class of agents, developed to enhance glutamatergic function, are the AMPA-positive modulators termed AMPAkines [107], a family of compounds that act by increasing the peak and duration of GLU-induced AMPA receptor-gated inward currents [66]. AMPA receptor function facilitation by AMPAkines should enhance indirectly, in a use-dependent fashion, NMDA receptor-mediated long-term potentiation, a variant of synaptic plasticity widely regarded as a substrate of memory [32]. Overall, AMPAkines enhance glutamatergic activity in the cortex, stimulate memory-dependent processing in animal models and improve, acutely, memory capabilities in both young and aged humans without any apparent serious side effects [65,67-69]. Consequently, AMPAkines are under development at present for treatment of cognitive dysfunction in various neuropsychiatric disorders.

As AMPA receptors function in concert with NMDA receptors, AMPAkines have also been proposed as potential therapeutic agents for schizophrenia. When added to low doses of clozapine, or conventional antipsychotics, AMPAkines synergistically block methamphetamine-induced rearing behaviour, which is an effect believed to predict antipsychotic efficacy [70]. Moreover, AMPAkines may induce DSR release into synapses by glia in response to their stimulation of AMPA receptors [71], thus contributing to increased NMDA receptor function and enhanced therapeutic effects.

1-(quinoxalin-6-ylcarbonyl) piperidine (CX-516, Cortex Pharmaceuticals, Organon) is the first AMPAkine to reach Phase I trials in schizophrenia. So far, the results of a pilot, double-blind trial in which patients taking clozapine were randomised to receive either CX-516, ≤ 900 mg t.i.d., or placebo for 4 weeks have been published [68]. Eighteen schizophrenia patients participated in this study and significant CX-516-induced improvements in cognitive and negative symptoms were reported. The only possible treatment-related side effect was hypertension, which was seen in one patient. CX-516 ≤ 1200 mg t.i.d. has also been assessed with no clear benefit in a small study (n = 8) as monotherapy for schizophrenia patients partially refractory to treatment with traditional neuroleptics [69]. At present, a more powerful compound with improved pharmacological properties (CX-717, Cortex Pharmaceuticals, Organon) is examined as adjuvant treatment for schizophrenia in a larger-scale study and additional, structurally distinct, AMPA receptor modulators are being developed by various research groups [67]. Furthermore, the NIMH-sponsored network entitled Treatment Units for Research on Neurocognition in Schizophrenia (TURNS) has recently selected the AMPAkine CX-619/ORG-24448 (Cortex Pharmaceuticals, Organon) as one of the first compounds to undergo testing as part of its efforts to facilitate the development of medications for enhancing neurocognition. The TURNS programme represents an innovative initiative that aims to identify compounds of interest and conduct proof-of-concept clinical studies on the treatment of cognitive deficits in schizophrenia [201].

5.3 mGluR modulators

mGluRs are G protein-coupled receptors that are divided into three groups and include eight subtypes termed mGluR1 – 8. Group I receptors function predominantly to potentiate both presynaptic GLU release and postsynaptic NMDA neurotransmission, with mGluR5 receptors showing significant colocalisation with NMDA receptors in rodents. Group II and III receptors, in general, serve to limit GLU release, particularly during conditions of GLU excess. Thus, group I agonists or positive modulators would be expected to stimulate NMDA receptor-mediated neurotransmission, and group I antagonists to inhibit it. In contrast, group II/III agonists or positive modulators would be expected to inhibit presynaptic GLU release [10,12,72]. Development of mGluRs modulators as therapeutic targets in schizophrenia is thus based on two alternative conceptualisations of the disorder. Effectiveness of group I agonists is predicted based on the models that postulate low NMDA receptor activity and/or GLU levels as being pathophysiological in schizophrenia, whereas use of group II/III agonists would follow models that postulate that GLU hyperactivity may be pathophysiological.

Preclinical studies have assessed the ability of group I (mGluR1, mGluR5) agonists to reverse effects induced by amphetamine, PCP and other psychotomimetics. The mGluR5 agonist 2-chloro-5-hydroxyphenylglycine has been found to reverse prepulse inhibition-disruptive effects of amphetamine in rodents. Similarly, both nonselective and group I-selective agonists inhibit PCP-induced DA release in rodent prefrontal cortex [10,12]. Several high-affinity agonists have been developed, including (-)-2-oxa-4-amino-bicyclo[3.1.0.]hexane-4,6-dicarboxylate (LY-379268) and the related compound LY-354740 (Eli Lilly), that permit characterisation of the effects of group II agonists in both preclinical and clinical studies. An initial study with LY-379268 demonstrated its ability to block PCP-induced increases in prefrontal GLU, along with PCP-induced impairments in working memory. Similarly, LY-3279268 has been shown by a variety of groups to inhibit PCP-induced hyperactivity during both acute and repeated administration, and reverse PCP-induced behaviours in monoamine-depleted mice [72]. A recent study

also suggests that LY-354740 may reduce working memory impairments and, perhaps psychotic symptoms transiently produced by ketamine in healthy human subjects [10].

Based on the effect of group II agonists on prefrontal glutamatergic hyperactivity, it has been proposed that these agents may be therapeutically beneficial in treating persistent cognitive deficits in schizophrenia [72,73]. At present, however, the degree to which psychotomimetic effects of PCP are related to alterations in glutamatergic versus dopaminergic neurotransmission is not known [12]. Clinical trials with mGluR2 agonists may thus also help clarify pathophysiological mechanisms in schizophrenia.

Overall, in comparison with NMDA receptor-based approaches, mGluRs modulators are presently in relatively early stages of development as potential drugs for schizophrenia. Primate studies and clinical trials are warranted in order to validate this molecular target for the treatment of this illness.

5.4 Ion-channel blockers/GLU release inhibitors

Recently, two compounds, lamotrigine and riluzole, which are widely used for the treatment of epilepsy and amyotropic lateral sclerosis (ALS), respectively, have been proposed and are presently evaluated for schizophrenia treatment, mainly on the basis of their ability to inhibit excessive presynaptic GLU release.

5.4.1 *Lamotrigine*

Despite limited supporting data for this application, anticonvulsant agents are widely prescribed to enhance the efficacy of antipsychotic drugs in schizophrenia [74]. Lamotrigine (3,5-diamino-6-[2,3-dichlorophenyl]-1,2,4-triazine) is a novel antiepileptic drug that is chemically unrelated to any currently available anticonvulsant medication. It has been extensively evaluated and is commercially available for the treatment of epilepsy [108]. Furthermore, lamotrigine is effective in the treatment of affective disorders [75] and, in addition to its mood-stabilising properties, significant quality of life and cognitive function improvements were reported with this drug in epilepsy [76] and Alzheimer's disease [77].

Lamotrigine reduces GLU release via blockade of voltage-dependent ion channels, particularly sodium channels and P- and N-type calcium channels and an outward potassium channel [78]. Thus, it was hypothesised that lamotrigine would attenuate those effects induced by NMDA receptor noncompetitive antagonists that are mediated by disinhibition of GLU release [10]. Consistent with this hypothesis, it was found that lamotrigine pretreatment reduces ketamine-induced psychosis, negative symptoms, and dissociation-like perceptual alterations, and increases the euphoric or stimulatory effects of ketamine in healthy humans [79]. Furthermore, lamotrigine showed efficacy in two animal models that may have predictive therapeutic value in schizophrenia: NMDA receptor antagonist-induced neurotoxicity [36] and NMDA receptor antagonist disruption of prepulse inhibition of the startle response [80].

So far, clinical trials with lamotrigine in schizophrenia have focused on the augmentation of clozapine treatment in refractory patients. In three open-label series [81-83] lamotrigine adjuvant treatment (100 – 300 mg/day) induced significant (≤ 75%) symptom reductions in clozapine-maintained, treatment-resistant patients. In a randomised, controlled, 14-week study performed with 34 male, forensic schizophrenia inpatients resistant to conventional neuroleptics and clozapine treatment, the addition of lamotrigine ≤ 200 mg/day to clozapine regimens significantly improved positive and general psychopathology symptoms [84]. Recently, the results of the first controlled trial in which fixed dose lamotrigine 400 mg/day was added to ongoing treatment with conventional or atypical antipsychotics have been published [85]. The completers ($n = 32$) analysis in this pilot study indicated, following 10 weeks of lamotrigine treatment, significant mean reductions in positive (-42%, $p < 0.03$) and general psychopathology (-36%, $p < 0.03$) symptoms, whereas the negative symptoms cluster was not significantly affected. Larger-scale investigations of lamotrigine adjuvant treatment in schizophrenia are at present ongoing.

5.4.2 *Riluzole*

Riluzole is approved by the US FDA as a neuroprotective agent for use in ALS and, similarly to lamotrigine, inhibits voltage-dependent Na^+ channels, thus resulting in decreased GLU release [86,109]. It was the first medication to show some impact on survival for ALS patients and, due to its pharmacological characteristics, has been proposed for evaluation as possible treatment in a number of psychiatric disorders, including schizophrenia [109] and affective disorders [87]. Recent case studies reported beneficial riluzole effects in depression and obsessive-compulsive disorder [87,88]. Clinical trials are warranted in order to assess riluzole treatment effects in schizophrenia.

6. Development issues

On the basis of research done so far, a number of challenges may be predicted in the process of development of glutamatergic neurotransmission modulators for use in schizophrenia treatment. Main unresolved issues presently include the estimation and establishment of: i) primary symptom targets; ii) potential effects on cognition; iii) optimal adjuvant treatment regimes; iv) optimal dose ranges; v) characteristic side effects profiles; and vi) therapeutic effects for different types of patients and illness stages.

Different types of glutamatergic modulators may differ in terms of their characteristic therapeutic effects profiles. NMDA receptor-GLY site agonists (Table 3) and AMPAkines [68] may represent the prototypes for medications affecting mainly the negative symptoms and cognitive deficits domains. Therapeutic effects of GLY site agonists have also been reported against antipsychotic drug-induced EPS and tardive dyskinesia [51,52]. However, because no monotherapy trials with these agents have

yet been performed, it is not clear whether the relatively modest effects of GLY and DSR registered against positive symptoms reflect pharmacological limitations of this type of compounds, or a ceiling effect resulting from their addition to ongoing established antipsychotics. Clarification of this issue would further guide the hypothesised use of NMDA receptor modulators. On the other hand, trials performed so far with the GLU release inhibitor lamotrigine suggest a main effect of this type of compound on positive symptoms and general psychopathology, whereas negative symptoms were not significantly affected [84,85]. These preliminary findings require larger-scale replication in studies using well-defined outcome criteria. Furthermore, at both conceptual and practical levels they suggest the intriguing possibility of assessing combined glutamatergic treatments (e.g., GLY site agonist plus GLU release inhibitor) in schizophrenia treatment.

In general, the first-generation small clinical trials with glutamatergic modulators have assessed cognitive parameters on the basis of symptom scales (e.g., Positive and Negative Syndrome Scale) ratings. Although the results of some of these studies may be viewed as encouraging, cognitive symptom subscales are only poorly related to performance-based measures of cognitive capabilities. Consequently, comprehensive neurocognitive testing-based assessments of the effects of glutamatergic modulators on cognitive functions are warranted. State-of-the-art neurocognitive tests batteries are presently employed in ongoing multi-centre studies (e.g., IMSER, TURNS) and should be regarded as standard procedures in future studies in this field.

Glutamatergic agents may not work equally well in combination with all antipsychotic medications. In regard to GLY site agonists, the most significant therapeutic effects were registered when used in conjunction with conventional neuroleptics, whereas clozapine appears to stand apart from all antipsychotics (Table 3). Full GLY site agonists appear to be ineffective when used as adjuvants to clozapine [54-56], whereas partial agonists may even exacerbate symptoms [57]. In contrast, the prototypical AMPAkine CX-516 has been reported to be effective in combination with clozapine [68] and lamotrigine appears to be effective when prescribed in combination with this drug, whereas it may work less well in combination with other antipsychotics [83]. A better understanding of the mechanisms of action that account for the diverse outcomes of glutamatergic modulators/clozapine treatment regimens may help explain the unique therapeutic profile of clozapine and contribute to the development of glutamatergic treatment strategies in schizophrenia.

The optimal dose ranges at which glutamatergic agents may be used in schizophrenia are presently unknown. For example, GLY, DSR and sarcosine doses of > 60, 2.1 and 2 g/day, respectively, although potentially beneficial, have not yet been assessed. Lamotrigine doses of ≥ 200 mg/day were found to be effective in some studies [84,85], but were also reported as detrimental in comparison with lower dosages [10]. Dosage issues require further research and are related to the establishment of the side effects profiles of glutamatergic modulators. Overall, these drugs seem to be practically devoid of the characteristic motor and metabolic side effects occasionally encountered with conventional and atypical antipsychotics. However, further studies are needed in order to consolidate these observations and monitor specific areas of concern. Although significant clinical or laboratory-determined side effects, including DSR kidney function effects [52], have not yet been reported with GLY site agonists, and GLY and DSR have been reported to actually decrease EPS severity [51,52], additional studies are clearly required in order to address long-term safety issues connected with the administration of this type of compound. Concerning lamotrigine, benign and serious rash are known side effects. Calabrese *et al.* [89], after reviewing the prospectively collected data from double-blind studies of lamotrigine in the treatment of mood disorders (n = 1198), reported that the risk of serious rash was nil. The rate of benign rash was determined to be 8%. This is on par with lamotrigine postmarketing experience, which has shown that the risk of rash is essentially limited to the first 8 – 12 weeks of treatment and can be limited by adhering strictly to the currently recommended slow initial rate of dose titration. Although the data furnished by Calabrese *et al.* [89] is encouraging, the prescribing information for lamotrigine nonetheless reports an overall 3% risk of Steven–Johnson syndrome in adults [90] and the occurrence of both benign and serious forms of rash should be carefully monitored in future studies involving schizophrenia patients.

Until now, glutamatergic treatments have generally been assessed mainly in chronic patients characterised by long illness duration, prominence of negative symptoms and paucity of positive symptoms and EPS. Further studies are needed in order to explore the possible benefits of glutamatergic modulators for patients with different symptom profiles and for patients in which predictors of treatment response (e.g., low GLY serum levels), as suggested in previous studies, may be evidenced. An additional and potentially promising domain in which the use of glutamatergic, especially NMDA receptor, modulators should be assessed, involves secondary prevention of disease (i.e., tackling of schizophrenia manifestations at a prodromal or relatively early stage of illness).

Ultimately, as highlighted by Krystal *et al.* [10], an additional challenge facing the development of glutamatergic compounds for schizophrenia may be economic and regulatory. Overcoming these inherent difficulties would require the willingness of the pharmaceutical industry to explore a path of high financial risk, involving the development of schizophrenia medications that are characterised by molecular mechanisms not explored so far and that may not be sufficient as stand-alone pharmacotherapies.

7. Expert opinion

Despite major advances in antipsychotic medications, there is clearly a need for innovative treatment strategies in schizophrenia that will ensure increased effectiveness against negative symptoms and cognitive dysfunction, ultimately

leading to disease outcome modification. Within this framework, mainly from a conceptual perspective at present, modulators of glutamatergic neurotransmission seem to have the potential for becoming clinically useful compounds to be used in daily practice.

The neurotransmitter role of GLU was definitively established only in the 1970s and GLU receptors were not differentiated until the 1980s. Consequently, drug development focusing on glutamatergic neurotransmission is historically and substantially behind that for other neurotransmitter systems. Nevertheless, two basic considerations are encouraging in the context of this complex endeavour. First, available data suggest, mainly for NMDA receptor agonists with which most clinical research has been done, that glutamatergic modulators may represent a distinct, new class of medications. This hypothesis is based on the fact that these types of compounds differ from both conventional and presently available atypical antipsychotics not only in terms of their mechanisms of action, but also in terms of their characteristic therapeutic and side-effect profiles. Furthermore, if glutamatergic modulators will eventually be established as effective against negative and/or cognitive symptoms in schizophrenia, it is reasonable to predict that, similarly to antipsychotics, their use will not be limited to this illness, but will encompass a variety of disorders in which these or similar symptoms clusters play a prominent role. For example, the usefulness of glutamatergic treatments has already been proposed and/or is being assessed in neurodegenerative disorders, autism, post-traumatic stress disorder and depression.

Specifically for the NMDA receptor, the GLY regulatory site is a promising target, with GLY site agonists currently in active development as schizophrenia treatments. However, due to intertwined efficacy and pharmacokinetic limitations, it is unlikely that GLY or DCS will become widespread treatments. DSR, if proven to be safe and significantly effective in future studies, has the potential to be recommended at least as add-on pharmacotherapy in schizophrenia. The advantages of this compound include the relative low dose requirements and the fact that it probably represents the natural neurotransmitter acting at the GLY site with no other known site of action throughout the nervous system. Furthermore, as with monoamine and acetylcholine systems, synthetic and degratory enzymes and especially neurotransmitter reuptake systems (e.g., by use of GLYT1 inhibitors), may prove highly effective psychopharmalogical development targets. More recently described DSR and SNAT transporters may serve as additional targets. It may ultimately be possible to develop ligands which, by virtue of contrasting affinities and/or efficacies, preferentially modulate specific populations of GLY site/NMDA receptor subtypes that may be differentially involved in schizophrenia.

Positive allosteric AMPA receptor modulators have been developed and are undergoing clinical development in schizophrenia (mainly for cognitive dysfunction) and other neuropsychiatric disorders. Direct agonists, antagonists and allosteric modulators have been developed for group I and II mGluRs and are undergoing clinical development for both schizophrenia and anxiety disorders. As with NMDA receptor modulators, many of the key compounds required for both preclinical and clinical testing in these areas remain proprietary. As these compounds become more generally available, it is expected that progress in development of glutamatergic therapies will further accelerate.

Preliminary clinical evidence suggests that the novel anticonvulsant lamotrigine, which inhibits excessive GLU release, may augment antipsychotic efficacy in some patients diagnosed with schizophrenia. However, replication of these findings is required before the possible inclusion of lamotrigine, along with carbamezepine and valproate, among the antiepileptic drugs used as add-on therapy in schizophrenia. In the case of riluzole, clinical data are pending.

Hypothetically, due to their therapeutic profile and to the role of GLU in brain physiology and development, glutamatergic modulators may, if proven effective, enrich the scope of pharmacological treatment in schizophrenia. New areas of investigation likely to be explored during the next years would include their use in maintenance treatment, with resulting limitation of exposure to antipsychotic drugs side effects and/or as early or 'preventive' treatments to be assessed during prodromal stages and/or following first psychotic episode in schizophrenia.

It should be stressed that no glutamatergic modulator has yet reached the market, and conclusive experimental and clinical research is still needed to more fully appreciate the potential role of these types of compound in schizophrenia management. Nevertheless, although the full range of benefits and limitations of these compounds remains to be demonstrated, glutamatergic treatments presently represent one of the most hopeful avenues for development of innovative pharmacological strategies in schizophrenia.

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